DESIGN AND STATISTICAL OPTIMIZATION OF GASTRIC FLOATING MATRIX TABLETS OF FAMOTIDINE USING POLYETHYLENE OXIDE AND GLYCERYL BEHENATE

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Ideally, an oral controlled drug delivery system releases the drug at a constant and reproducible rate despite varying conditions. An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity and composition of the gastrointestinal fluids as it passes down the gastrointestinal tract (GIT). Many efforts have been made to design oral controlled drug delivery systems that deliver the drug at a constant rate as it passes down the GIT. In spite of constant rate of release of drug from the dosage form it may not be absorbed uniformly over the length of the GIT. Drug absorption from the colon is usually erratic and inefficient and also, certain drugs get absorbed only from the stomach or the upper parts of the small intestine.

Furthermore, an important factor which may adversely affect the performance of an oral controlled drug delivery system is the gastric transit time. More particularly, in instances where the drug has clear-cut "absorption window" i.e., the drug is absorbed only from the specific regions of the stomach or upper parts of the small intestine, absorption may not be complete with a typical oral controlled drug delivery system in which it is rapidly transported due to less gastric transit time. It is apparent that, for a drug exhibiting "absorption window", an effective oral controlled drug delivery system is needed not only to deliver the drug at a controlled rate but also to retain the drug in the upper parts of the GIT for a long period of time.

Various approaches have been made to retain the dosage form in stomach as a way to increase the overall gastric retention time which include high density systems, floating systems, expandable, unfoldable and swelling systems, super porous hydrogels, bioadhesive systems, magnetic systems, osmotic regulated systems and use of passage delaying agents.

Out of these approaches, gastric floating drug delivery is considerably an easy and logical approach in the development of gastric floating drug delivery systems (GFDDS). These systems have density lower

than gastric fluids (normally less than one) and remain buoyant in the stomach contents which seem to be useful for drugs primarily absorbed in the stomach, duodenum, and upper jejunum segments. The GFDDS are able to prolong the retention time of a dosage form in the GIT, thereby improving the oral bioavailability. However, these GFDDS are suitable for delivery of drugs over a period of 12 hours as the gastric retention of any material lasts normally for a period of 6-10 hrs.

Famotidine, a histamine H_2-receptor antagonist, is widely used in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro oesophageal reflux disease and erosive oesophagitis. The plasma half life of the drug is 2.5-3.5 hrs as reported in literature, hence multiple doses are needed, which leads to patient incompliance and fluctuations in plasma concentration. The recommended adult oral dose of famotidine is 20 mg twice daily or 40 mg once daily. The effective treatment of erosive oesophagitis requires administration of 20 mg of famotidine 4 times a day. Gastric acid secretion in case of ulcers cannot be inhibited beyond 5 hrs with a conventional dose of 20 mg of famotidine. An alternative dose of 40 mg leads to plasma fluctuations; thus a sustained release dosage form of famotidine is desirable.

Additionally, famotidine is not absorbed uniformly throughout the gastrointestinal tract (GIT) but mainly at a specific absorption site (stomach and upper part of small intestine) leading to incomplete and variable absorption (bioavailability is 40-50%). Thus, a dosage form achieving gastric retention, thereby presenting the system at absorption site over a prolonged period is beneficial for improving bioavailability, minimizing wastage and side effect is highly desirable. Moreover, being a weak base, famotidine with a pK_a of 7.06 has pH dependant solubility (maximum solubility at acidic pH) and its gastric retention would allow adequate time for its dissolution, the rate limiting step in drug absorption. In view of these unique absorption characteristics, the gastric residence time of famotidine formulation should be prolonged to permit famotidine to reach the site of absorption in a controlled manner so as to increase its oral bioavailability. Hence famotidine was chosen as a drug of choice for

developing GFDDS with both effervescent and non-effervescent approaches.

The main aim of the present investigation is to design and statistically optimize GFDDS of famotidine using two approaches i.e. effervescent and non-effervescent by using polyethylene oxide (PEO) and glyceryl behante (GB) respectively for releasing the drug over a period of 12 hrs.

The objective of the present investigation include studies on (a) Calculation of immediate and maintenance doses of the famotidine for proposed EGFMT and NEGFMT and prediction of theoretical profile, (b) Development and evaluation of PEO based effervescent gastric floating matrix tablets (EGFMT) of famotidine using sodium bicarbonate as gas generating agent, (c) Development and evaluation of non-effervescent gastric floating matrix tablets (NEGFMT) of famotidine using GB, (d) Optimization of prepared EGFMT and NEGFMT for the release of famotidine over a period of 12 hrs, (e) Optimization of polymer concentration, effervescent agent concentration and other ingredients based on the evaluation parameters like floating lag time, floating time and matching of drug release profile with the theoretical profile using statistical optimization technique like response surface methodology in full factorial design, (f) Evaluation of drug and excipient interaction studies of the optimized product and their stability as per ICH guidelines, (g) *In vivo* floating ability of the selected optimized GFMT by X-ray evaluation and (i) *In vivo* performance of the selected optimized GFMT.

PEO, a nonionic homopolymer of ethylene oxide, is available in different molecular grades. PEOs are mostly used to produce controlled release solid dosage forms such as matrices, reservoirs or coated cores. PEOs control the release of the active moiety either by swelling (large molecular weight, >2 MDa) or by eroding and swelling (small molecular weight, <0.9 MDa), forming a hydrogel in water. There are only few reports on the use of PEO in the design of GFDDS and no reports in the development of famotidine GFDDS. Hence, PEO is proposed for the development of effervescent gastric floating matrix tablets (EGFMT). As

molecular weight of PEO is critical in the control of drug release two grades of PEO (WSR 303 and WSR N-12K) are chosen for the design of EGFMT of famotidine. The molecular weight of WSR 303 and WSR N-12K are 7 MDa and 1 MDa respectively. The viscosity of the PEO depends on the molecular weight and the viscosity of WSR 303 for 1% solution is 7,500–10,000 cps and that of WSR N-12K is 400-800 cps for 2% solution.

Glyceryl behenate (GB) is an insoluble, non-swelling, matrix forming wax material. It is a mixture of glycerides of fatty acids, mainly behenic acid, originally introduced as a lubricant in tablet and capsule manufacturing. It has been used in the preparation of sustained release tablets and as a matrix forming agent for the controlled release of water soluble drugs. It is having a density of 0.942 g/cm^3 which is less than the density of gastric fluids. There are no reports on the use GB for the development of GFDDS. Hence it is proposed to study its applicability in the design of non-effervescent gastric floating matrix tablets (NEGFMT) of famotidine because of its capability to control drug release as well as low density of the polymer.

The thesis consists of Five Chapters. **Chapter-I** includes introduction to gastric retentive drug delivery systems and methods for increasing gastric retention time for drugs having specific absorption sites, advantages, disadvantages and limitations of these methods. Brief review of past work on gastric floating drug delivery systems is also given. Brief review on statistical approaches for design and optimization of formulation was given.

The drug selected to evaluate the role of gastric floating matrix tablets (GFMT) in improving the oral bioavailability is famotidine. Brief profiles of this drug and analytical methods used in the present investigation are described in **Chapter II**. Profiles of PEO and GB are given in this chapter along with their interference study with famotidine. Calculation of loading, maintenance dose and total dose of famotidine and prediction of theoretical release profile is also given.

There are no sustained or controlled release dosage forms for famotidine and hence the initial and maintenance doses of the drug required was calculated based on the pharmacokinetic properties using Robinson and Eriksen equation using the assumption of zero order release from the dosage form and the calculated dose was found to be 49.05 mg which was rounded to 50 mg. The theoretical release profile was predicted based on the zero order release characteristics and an amount of 8.57 mg to be released in the first hour as initial dose followed by the release of 3.68 mg/hr for the remaining period of 11 hrs as maintenance dose.

Design and statistical optimization of effervescent gastric floating matrix tablets (EGFMT) by using PEO WSR 303 and PEO WSR N-12K of famotidine is given **Chapter III**. Drug-excipients interaction studies (FTIR, DSC and XRD) and stability studies of optimized EGMFT are also given in this chapter.

A 3^2 full factorial design was used with 2 factors and 3 levels and experimental trials were performed using all 9 possible combinations. The amount of polymer (X_1) at 50, 100 & 150 mg levels and percent of sodium bicarbonate (X_2) at 10, 15 & 20% to the total weight of drug and polymer levels were selected as independent variables. According to established theoretical profile, 18% of drug release has to be achieved within 1 hr and complete drug release has to occur over a period 12 hrs. Hence, two responses i.e. percent drug released in 1 hr Y_1 (%DR1) and time for 100% drug release Y_2 (T_{100}) were selected as dependent variables to optimize the response data.

ANOVA, multiple regression analysis (to obtain coefficient values in the equation), response surface plots and optimization of data was done by Design Expert (8.0.6.1, trial version). 5% level of significance ($p < 0.05$) was considered as significant.

The poor flow property of famotidine was changed to excellent flow with addition of PEO to the free drug powder and the flow was enhanced

with increase in their content indicating the suitability of physical mixtures for direct compression.

EGFMT were prepared using PEO (PEO WSR 303, PEO WSR N-12K) and sodium bicarbonate as gas generating agent by direct compression method. The prepared EGMFT showed good floating properties with the floating lag time of less than 20 sec and the total floating time was observed to be in the range of 8-24 hrs. The floating lag time was increased with increase in the polymer content whereas decreased with increase in the amount of sodium bicarbonate. This could be due to the entrapment of the generated gas in the polymer hydrogel enabling it to float. Additionally, decrease in the molecular weight and/or viscosity of PEO resulted in a decrease in floating lag time and total floating time. These results clearly indicated the influence of the viscosity of the polymer in maintaining the floating of the EGFMT.

Uniformity of weight, hardness, friability and uniformity of content of all the prepared EGFMT of famotidine were found within the official and fixed limits.

The results of dissolution data of all the prepared EGFMT indicated slow and sustained release of famotidine from WSR 303 and WSR N-12K based EGFMT. Dissolution data indicated that the higher viscosity (or molecular weight) grade WSR 303 delayed the drug release for extended period of time up to 23 hrs when compared to lower viscosity (or molecular weight) grade WSR N-12K, which controlled the release of the drug up to 12 hrs only. This behaviour could be explained that PEO particles of increasing viscosity (or molecular weight) will swell rapidly and produce swollen particles of smaller volume. The matrices made of particles of PEO with higher viscosity grade will contain pores of smaller diameters due to formation of hydrogel with higher gel strength which will slower drug release than those made up of PEO particles with lower viscosity grade.

Increased sodium bicarbonate resulted in relatively higher drug release. The increased amount of sodium bicarbonate caused a large

amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby rapid drug release.

The drug release from all the EGFMT followed zero order kinetics with anomalous (non-Fickian) diffusion.

Y_1 (%DR1) and Y_2 (T_{100}) were fitted to linear, interactive and quadratic models. A suitable polynomial model for describing the data was selected based on correlation (R^2) and PRESS values. Response Y_1 followed quadratic model and response Y_2 followed linear model for WSR 303 based EGFMT. Linear and quadratic models were followed by responses Y_1 and Y_2 respectively for WSR N-12K based EGFMT. Hence these models were selected for further optimization.

The selected models were found to be significant as indicated by the results of ANOVA (higher F-values and lower p-values) and a good correlation was observed between the independent and dependent variables. The respective polynomial equations were predicted and contour and response surface plots were drawn from the results of the 3^2 full factorial design using Design Expert 8.0.6.1 software of trial version. Contour and response surface plots clearly explained the influence of X_1 and X_2 on the responses. Optimized formulations were predicted using a multi-criteria decision approach, numerical optimization technique (desirability) and graphical optimization technique (overlay plots) with the following constraints: a) Y_1 (%DR1) = 18% and b) Y_2 (T_{100}) = 12 hrs, which were obtained from the theoretical profile. The f_1 values of optimized formulations were very close to the '0' and f_2 values were more than the '50' indicating the similarity between the optimized formulations and theoretical profile. The release of drug from the optimized formulations followed zero order with anomalous (non-Fickian) diffusion mechanism. The efficiency of prepared optimized formulations (W_{opt} and N_{opt}) were tested by using the %RE values between experimental and predicted responses and which were found to be less than 5%.

The drug-excipients interaction studies (FTIR, DSC and XRD) indicated no chemical interaction between the famotidine and excipients used but indicated physical interaction between the drug and excipients.

The results of the long term and accelerated stability studies as per ICH guidelines conducted on the optimized formulations indicated no significant change in floating lag time, total floating time, uniformity of weight, hardness, uniformity of content and drug release was found to be consistent.

Chapter IV consists of design and statistical optimization of non-effervescent gastric floating matrix tablets (NEGFMT) by using GB along with drug-excipients interaction studies and stability studies of optimized NEGMFT.

Two methods of preparations were employed i.e. 1) direct compression of physical mixtures (FPM) and 2) compression of melt granules obtained from hot fusion technique (FMG). Lactose was employed as channeling agent to study the effect on drug release. GB being a hydrophobic polymer, the effect of channeling agent was studied on the drug release and lactose was chosen being soluble in nature. Hence the concentration of lactose was chosen as an independent variable along with concentration of GB to assess its effect on drug release and studied at three levels viz. 0, 5 and 10%. Similar design that used for EGFMT was used for NEGFMT with GB and lactose as X_1 at 25, 50 and 75 mg levels and X_2 at 0, 5 and 10% levels respectively for each method of preparation and %DR1 and T_{100} as response Y_1 and Y_2 respectively.

With the addition of GB to the free drug powder, the poor flow property of drug was changed to good flow and the flow was enhanced with increase in GB content indicating the suitability of physical mixtures for direct compression. The melt granules prepared with drug-GB mixtures also exhibited good flow characteristics indicating their suitability for compression.

All the prepared NEGFMT floated immediately after placing into the beaker and the floating was maintained more than 24 hrs. This might be

due to low density of the tablet with the presence of low density waxy material (GB), which produced an upward motion of the dosage form and maintained its floating.

Uniformity of weight, hardness, friability and uniformity of content of all the prepared NEGFMT of famotidine were found within the official and fixed limits.

In GB based NEGFMT, a considerable retardation of drug release was observed with increasing the GB content and retardation was more for formulations prepared from melt granules obtained from hot fusion technique when compared to formulations prepared from physical mixtures. Increasing the concentration of channeling agent enhanced the drug release from the hydrophilic matrix of NEGFMT. The T_{100} values of the NEGFMT prepared from both methods were increased with increase in GB and decreased with increase in lactose content and higher T_{100} values were obtained for NEGFMT prepared with melt granules of hot fusion technique than the physical mixtures. The drug release from all the EGFMT and NEGFMT followed zero order kinetics with anomalous (non-Fickian) diffusion.

Response Y_1 was found to follow linear model and response Y_2 was found to follow quadratic model for NEGFMT prepared from physical mixtures. The responses Y_1 and Y_2 were found to follow quadratic and interactive model respectively for NEGFMT prepared from melt granules. Hence these models were further subjected for optimization.

Similar procedure as described in Chapter III was followed for analysis and optimization of NEGMT. The release of drug from the optimized formulations followed zero order with anomalous (non-Fickian) diffusion mechanism. These optimized formulations (FPM_{opt} and FMG_{opt}) were found to be similar to theoretical release profile as indicated by lower f_1 values and higher f_2 values.

There were no interactions observed between the famotidine and excipients from drug-excipients interaction studies (FTIR, DSC and XRD). The results of the long term and accelerated stability studies as per ICH

guidelines conducted on the optimized formulations indicated no significant change in floating lag time, total floating time, uniformity of weight, hardness, uniformity of content and drug release was found to be consistent.

In vivo floating ability using X-ray photography and pharmacokinetic evaluation of the selected optimized GFMT are given in the chapter **V**.

All the four optimized formulations (W_{opt}, N_{opt}, FPM_{opt} and FMG_{opt}) were found to be similar with the theoretical release profile, however, W_{opt} and FMG_{opt} respectively consumed less than half the quantities compared to N_{opt} and FPM_{opt}. Hence, W_{opt} and FMG_{opt} were selected for *in vivo* studies. These selected statistically optimized formulations of famotidine were prepared with radio opaque agent and evaluated for the *in vivo* floating ability using X-ray photography. The products were buoyant for about 6 hrs in fed state compared to fasting state in which they were buoyant for 3 hrs.

There are no commercial gastric floating systems or sustained release products for famotidine and hence, commercial immediate release formulation, Fadine 20 was compared with the experimental formulation as reference for *in vivo*.

There is a significant increase in the oral bioavailability of the famotidine from W_{opt} and FMG_{opt} which was evident from the increased AUC (~2 times) than that of commercial formulation. There was no significant difference in C_{max} values among Fadine 20, W_{opt} and FMG_{opt}. The *in vivo* data demonstrated that the experimental formulations (W_{opt} and FMG_{opt}) exhibited longer T_{max}, $t_{1/2}$ and MRT values than commercial formulation, which indicated that experimental formulations followed sustained release pattern compared to marketed immediate release formulation.

The minimum effective concentration of famotidine was reached for both the optimized formulations within 15 min and maintained up to 15-17 hrs. Immediate release commercial formulation also attained the

minimum effective concentration within 15 min and maintained up to 6 hrs only. Approximately a three fold increase in the duration of action was observed in the designed floating matrix tablets in which the initial dose was released on par with the immediate release dosage form followed by a sustained release of drug over 15-17 hrs.

A good IVIVC was obtained with level A correlation for experimental formulations except for commercial formulation. Hence, it was concluded that *in vitro* data was perfectly coinciding with the *in vivo* performance that was observed.

The summary of the research work and conclusions drawn were given at the end of the thesis. Results of the present study clearly indicated that effervescent and non-effervescent based GFMT of famotidine were successfully designed and optimized by using PEO and GB respectively. These systems were retained in the stomach for longer periods during fed state and released the drug in a sustained manner. Hence, the developed gastric floating systems can provide a sustained release effect with good oral bioavailability for drugs like famotidine that are having site specific absorption in the stomach or the upper parts of the small intestine.

The source of information of references cited in thesis is given at the end of each chapter. Overall the entire thesis covers a brief introduction, a detailed description of the experimental methods, results and discussions.